Andrx
PHARMACEUTICALS, INC.

Doc No 189328

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 85N-0214 180-Day Generic Exclusivity for Abbreviated New Drug Applications, 64 Fed. Reg. 42,873 (August 6, 1999)

Ladies and Gentlemen:

Andrx Pharmaceuticals, Inc. ("Andrx") submits the following comments on the regulations recently proposed by the Food and Drug Administration ("FDA" or the "Agency") concerning the generic marketing exclusivity period provided for under 21 U.S.C. §355(j)(5)(B)(iv). Andrx believes that certain of the proposed provisions are well conceived and provide useful clarification. We also perceive, however, that other proposed provisions intended to prevent prolonged or indefinite delays in the commercial marketing of generic drug products ("Protracted Marketing Delay") are inconsistent with the statutory language and do not promote its underlying legislative purposes.

The statute created the 180-day exclusivity period, an officially sanctioned head start, as an economic incentive for companies to challenge the patent(s) listed by the NDA holder. This is a "Mandated Reward" for a successful challenge. See Mova v. Mylan, 140 F. 3d 1060, 1066 n.6 (D.C. Cir. 1998). Any regulation ultimately adopted should balance the goal

85N-0214

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of providing the Mandated Reward and avoiding Protracted Marketing Delay, but must do so in a manner that is consistent with the clear language of the statute.

We set forth below our thoughts on the legal and policy infirmities of the proposed regulations, and we offer our suggestions on how those regulations and the Agency's procedures for processing ANDAs may be modified to better preserve the Mandated Reward, without Protracted Marketing Delay'.

1. Assuming That FDA Has Authority To Create "Triggers" Not Identified In The Statute, The Regulations Should Clarify That The "Triggering Period" Does Not Commence Until An Alternative Product Has Received "Tentative Approval."'

Andrx agrees that the regulations should impose reasonable limitations on the potential reward of exclusivity that will eliminate the possibility of its use as an indefinite roadblock to a generic product that might otherwise be marketed by a subsequent applicant. There are various ways to accomplish this objective. FDA has chosen to create "triggers" not identified in the statute. For purposes of this comment, we assume at this time that the proposed provision is within the Agency's rulemaking authority. Thus, our only comment

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1 Andrx intends to submit additional comments, either alone or as part of its trade association, concerning other mechanisms to curtail potential abuses of the exclusivity award.

2 As this term is also commonly applied to ANDAs that have been tentatively approved by the Agency from a scientific standpoint, but which can not be approved for marketing until the expiration of the 30 month period described in section 505(j)(5)(B)(iii) of the Act, Andrx believes that the regulations should utilize an alternative term -- such as Pending Approval -- when describing an ANDA that would be approved "but for" a previous applicant's exclusivity rights.

on this part of the proposal is that there is a potential inconsistency between the definition of the triggering period in Section II.B. 1 and the discussion of the length of the triggering period in Section II.B. 1 .a.

For the most part, the proposal makes clear that in no case does the triggering period begin before "a subsequent ANDA applicant with a paragraph IV certification receives tentative approval stating that but for the first applicant's exclusivity, the subsequent ANDA would receive final approval". 64 Fed. Reg. at 42,877. However, in defining the length of the triggering period, the proposal states that the triggering period "would follow one of the following: (1) The tentative approval of a subsequent ANDA with a paragraph IV certification for the same drug product, (2) expiration of a 30-month stay of ANDA approval due to patent litigation, (3) expiration of a preliminary injunction prohibiting marketing of an ANDA product, or (4) expiration of the statutorily described exclusivity periods for the listed drug." Id. at 42,878. If, after reviewing all comments, the Agency remains persuaded that its proposed new triggers are authorized and reasonable[3], Andrx suggests the following revision to avoid future confusion: If the first applicant is faced with patent litigation, the

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3 Andrx understands the dilemma faced by the Agency in attempting to promulgate regulations which will (i) avoid Protracted Marketing Delay, (ii) provide the Mandated Reward, and (iii) be upheld by the courts, when the appropriateness of those regulations are litigated. While this dilemma is very similar to the uncertainties faced by an applicant when it makes a Paragraph IV Challenge (as defined below), the consequences are very different. If its regulations are not upheld, the Agency can continue its practice of regulating directly from the statute. If an applicant chooses to market its ANDA product and then its position on the patent is not upheld, that applicant's continued existence may be in jeopardy.

triggering period will not begin to run until the later of(i) the expiration of the 30-month stay of the prior applicant's ANDA approval due to the pendency of patent litigation or any preliminary injunction which prohibits the marketing of its product following the Agency's approval of that ANDA, and (ii) the tentative approval [or Pending Approval, using our suggested terminology] of a subsequent ANDA with a paragraph IV certification for that same drug product.

2. Exclusivity Should Not Be Limited To The First Filer Of A Paragraph IV ANDA. If That Filer Can Not Or Does Not Cause A Generic Product To Be Commercially Marketed, Exclusivity Should Be Provided To The First Such Applicant That Is Prepared And Able To Engage in Commercial Marketing Without Delay.

Congress provided an incentive to generic applicants to challenge and tear down unjustified patent barriers to drug price competition by rewarding certain ANDA applicants who seek to market generic products prior to the expiration of their listed patents (a "Paragraph IV Challenge"). By limiting exclusivity to the first ANDA applicant that makes a Paragraph IV Challenge, the proposed regulations fail to achieve the Agency's stated goal of balancing the grant of that Mandated Reward against the possibility of Protracted Marketing Delay. The proposed regulations are focused, almost exclusively, on elimination of exclusivity for ANDAs that do not beat the clock (the "triggering event"). Indeed, if the first applicant cannot be approved, or cannot or will not engage in commercial marketing, the proposed regulations eliminate the Mandated Reward instead of providing a continuing

incentive to reward a subsequent applicant that succeeds in being the first to make a generic product available.

As will be further discussed in this commentary, certain events or considerations might prevent or preclude the first applicant from being able to make a generic product commercially available within the triggering period. In these circumstances, Andrx believes that Congress' intent -- of providing the Mandated Reward -- is best achieved by granting marketing exclusivity to the applicant whose Paragraph IV Challenge succeeds in making that applicant the first to bring a product to market (the "Successful Applicant"). That exclusivity award may be made because an applicant overcame a patent barrier through a court determination, because it was able to achieve the dismissal or settlement of its patent infringement case or because no suit was ever filed against such applicant.

Limiting exclusivity to the first Paragraph IV applicant is an outcome not dictated by the statute. Even the proposed regulations acknowledge that the statute may be read as permitting "rolling exclusivity." Assuming such a limitation is permitted, the question must be asked, is this a wise position to adopt? We think not.

The Agency determined to reward only the first applicant to make the Paragraph IV Challenge because, in its view, to do otherwise "would further delay the entry into the market of generic drug products with no countervailing public benefit." Were this FDA assessment theoretically correct, which we do not concede, the Agency cannot, as a matter of law, and should not, as a matter of policy, eliminate or unduly restrict the Mandated Reward simply

because it desires to foster more rapid entry of generic products into the marketplace.[4] Congress enacted the Mandated Reward provision for the generic company that, as a "previous" applicant under 21 U.S.C. § 355(j) (5) (B) (iv)is able to invent around or litigate past the reference drug's patents.[5]

In making a Paragraph IV Challenge, a generic company is required to devote years of effort and invest millions of dollars in developing, preparing for the commercial manufacture of, and preparing to litigate and/or litigating patent issues concerning, the product it seeks to market. Beginning years before the NDA holder's patents expire, a generic company must: (1) research the pharmacokinetic and pharmacodynamic characteristics of the reference drug; (2) research the patents associated with the reference drug (both before and after it files its ANDA); (3) identify suitable bulk drug suppliers or develop new methods of manufacturing the active drug that will avoid process patents and, if applicable, polymorph patents, (4) create and be able to commercially manufacture a bioequivalent and stable formulation employing different technologies than the NDA holder, assuming the applicant's primary defense in the inevitable patent litigation will be

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4 Were the Agency able to do this, then NDA holders' patents -- an analogous "reward" granted to inventors -- could be similarly ignored, and presumably Congress would not have enacted the Paragraph IV Challenge procedure as a means to foster generic competition.

5 Congressional recognition of the benefits to be derived from incentives such as exclusivity can similarly be found in 21 U.S.C. § 355 A, which provides an additional 6-month period of exclusivity (after the expiration of patents) for conducting certain pediatric studies, as well as the current debate over "restoring" patent terms for certain "pipeline drugs".

non-infringement (if the applicant employs an invalidity defense in its Paragraph IV Challenge, it may duplicate the NDA holder's technology); (5) assemble and submit its ANDA; and (6) be prepared to and actually defend against the patent litigation which in most instances will be initiated by the NDA holder.

In some cases the NDA holder will initiate patent litigation to legitimately enforce its patent(s). In other instances, no matter how thorough (and legally correct) the ANDA applicant may be in demonstrating patent invalidity, noninfringement or unenforceability, the applicant will find itself in litigation instituted solely to extend the market life of the NDA holder's product. For as long as a court will allow it to maintain its lawsuit, the NDA holder can threaten the ANDA applicant with potential damages that could well exceed the gross revenues to be derived from the sale of the applicant's generic product (if it were to ultimately lose that litigation) or even the value of the applicant company itself. Whatever the NDA holder's motivation, a successful Paragraph IV Challenge ultimately benefits the public. We are loathe to believe that Congress envisioned an FDA committed to rationalizing the withholding of the exclusivity it provided as a Mandated Reward to the applicant that actually provides this public benefit.

The Mandated Reward is an appropriate incentive for the first ANDA applicant who encounters these obstacles, and prevails, thereby conferring the desired public benefit. Without that reward, Andrx (and presumably other similar companies) would seriously consider not being in this business. Moreover, the proposed regulations' elimination of that reward when (and because) another ANDA applicant was unsuccessful in its Paragraph IV

Challenge, could eliminate the societal benefit of generic competition precisely when it is most needed.

3. An Applicant Should Not Lose Exclusivity Solely Because It Reformulates Its Product In Order To Prevail In Its Patent Litigation.

The Agency has noted its concern that, "in the rush to be the first ANDA with a paragraph IV [certification], applicants will submit the results of the first completed bioequivalence study, whether or not the results meet the standards for approval." 64 Fed. Reg. at 42,875. Accordingly, it has proposed that "if the first applicant submits a new paragraph IV certification because, for example, it makes a formulation change requiring a supplement or an amendment to its ANDA, it may no longer be accorded first applicant status. If there is another applicant with a paragraph IV certification for the same drug product, the first applicant will no longer be eligible for 180-day exclusivity."

Although Andrx understands the Agency's concern that applicants may intentionally, or through dereliction, submit data that do not meet approval criteria, we note that there is no basis in our experience, and no cited basis in FDA's experience, to believe that applicants intentionally or irresponsibly submit data that perforce cannot be approved. This proposal is a remedy for a problem that does not exist.

Under applicable FDA policy, each ANDA is evaluated to determine whether it is sufficiently complete to warrant substantive review. This screening can identify bioequivalence studies that, on their face, are not adequate. Moreover, with few, if any,

exceptions bioequivalence studies are performed by third party contract research organizations ("CROs"). These CROs collect, analyze, and report upon the data. Criteria for determining whether a study demonstrates bioequivalence are established and well known to them. Unless the Agency is asserting impliedly that applicants and CROs are individually and collectively conspiratorial and untrustworthy, no basis exists for the Agency's proposed provision.

In fact, there are circumstances in which an ANDA applicant may find it advantageous or necessary to amend or supplement an ANDA -- not because of any obvious defect in the original filing, but as the result of intervening events and solely for the purpose of expediting Agency approval and/or resolution of patent claims that might otherwise delay marketing of the generic product.

The Agency has encountered such new submissions on at least two occasions: by Andrx, in connection with controlled release diltiazem (Cardizem® CD) and by Genpharm, in connection with form 2 ranitidine (Zantac®). There likely have been and will be other situations requiring new submissions because the Agency determines that the formulation and bioequivalence studies submitted by the ANDA applicant may not be approved. Andrx believes, and to that extent agrees with the Agency, that such submissions may present different issues which should result in different outcomes.

For example, the Andrx diltiazem ANDA was approved by the Agency without the need to conduct new bioequivalence studies. This was not a situation involving the Agency's declared concern, viz., Andrx did not "in the rush to be . . . first . . . [and] submit the results

of the first completed bioequivalence study, [without regard to] whether or not the results [met] the standards for approval." Notwithstanding approval of its initial formulation, Andrx was not in a position to market that formulation because of the patent infringement lawsuit still pending against it, Given the potential damages Andrx could incur if it were to market its product and lose that case, Andrx chose not to take the risk of marketing. As the Agency has previously noted, it would not be "prudent" for an applicant in that position to begin marketing its product. See Proposed Rules: Abbreviated New Drug Applications, 54 Fed. Reg. at 28,894 (1989); Abbreviated New Drug Application Regulations: Patent and Exclusivity Provisions, 59 Fed. Reg. at 50,352 and, 50,355 (1994).

Andrx chose to reformulate its approved product in order to market a generic product as soon as possible. It could have continued to engage in patent litigation, the pace of which would have delayed marketing of any generic product for at least two additional years[6]. The alternative strategy, product reformulation, proved successful and in the consumers' best interest, for it permitted Andrx to resolve the patent litigation on the same date that the Agency approved the sale of its reformulated product. Andrx commenced selling its product a few weeks later. This reformulation strategy did not in any way prevent or inhibit another

6 Had the Court ruled in favor of Andrx' position on the originally *approved* ANDA before its reformulated product was able to safely gain market access, Andrx could have withdrawn its amendment and begun to market its original product.

Successful Applicant from gaining access to the market'. In our opinion, such a strategy, because of its consequent public benefits, should not be precluded by the regulations*.

Reformulations undertaken because an ANDA product either has been determined to infringe the listed patent or is not approvable are not intended to and do not accelerate marketing of a generic product. They are salvage initiatives only. Andrx therefore agrees that previous applicants should lose exclusivity rights initially established when formulation changes are motivated by decisions of a court holding the listed patent to be infringed or because the FDA will not approve the formulation.

4. An Applicant Should Not Lose Exclusivity If It Is Required To Perform New Bioequivalence Studies Due To A Change In The Agency's Review Criteria.

Reformulation could be required by or result from regulatory changes made by the Agency. The following are some examples of past Agency changes of bioequivalence requirements. This history demonstrates that changes in the Agency's approval requirements for a given ANDA may well occur in the future:

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7 As the 'triggering period" concept will prevent this strategy from barring market access for a Successful Applicant beyond the period that the Agency recognizes is contemplated by the statute, there is no reason for the Agency to adopt this position in situations like the one encountered by Andrx.

8 Ironically, this proposal might have the affect of delaying the marketing of a generic, as the first applicant might choose not to reformulate its non-approveable product in order to avoid losing the ability to waive its exclusivity "right" in favor of a Successful Applicant.

- Conjugated Estrogens, where the approval requirements changed and a new guidance was issued in response to a Citizens Petition filed by or for the NDA holder,
- Metered-dose inhalers, where the approval requirements changed and a new guidance was issued following an Advisory Committee review, and
- Transdermal skin irritation studies, where the requirements changed following the issuance of a new guidance. FDA Draft Guidance for Industry issued February 1999, Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products.

If an applicant were required to conduct new or additional studies based upon changed study acceptance criteria, there is no basis in the law or logic on which the Agency may or should deprive a Paragraph IV applicant of its statutorily granted right to exclusivity. Andrx agrees that new studies required to replace initially submitted bioequivalence studies, results of which obviously did not meet the Agency's approval standards at the time they were submitted, should cause an applicant to lose its status as the "previous" applicant entitled to exclusivity. Not all examples are so clear-cut, however. There are instances in which the deficiency is not apparent, or is debatable, and applicants choose to conduct replacement studies rather than spend time appealing an adverse decision. In such circumstances, FDA may and should exercise common sense and continue to reward or deny exclusivity based on the degree to which the deficiency was or should have been "obvious" to the applicant or CRO at the time of submission.

5. Both The Existing and Proposed Regulations Are Overly Restrictive In Their Treatment Of When A Late Issued Patent Is Untimely.

The existing regulations provide that, if an ANDA is accepted for filing prior to the NDA holder's submission of a listed patent to the Agency, the applicant is not required to certify to that patent. Recognizing that this "untimely" patent may still be a legal impediment to the marketing of that applicant's product, the proposed regulations recognize this one instance as an exception to its proposed rule that exclusivity be lost in the event of an ANDA supplement or amendment containing a formulation change which requires new bioequivalence studies.

Andrx believes that the regulations should provide exclusivity to any deserving applicant whose ANDA is affected by patents listed in the Orange Book after the date the applicant submits its ANDA to the Agency. To accomplish this goal, the regulations should incorporate a time frame which better reflects the ANDA process, i.e., whether a patent has been listed in the Orange Book on a timely basis should be determined by reference to the date the ANDA is submitted to the Agency (as opposed to the date such application is accepted for filing by the Agency) as well as the date FDA publishes the existence of the newly issued patent in the Orange Book.

As noted above, the process of developing a product that will be the subject of a Paragraph IV Challenge begins years before patent expiration. Once a formulation is developed that the applicant believes (and bioequivalence studies establish) is bioequivalent

to the brand, the applicant submits its ANDA to the Agency with a Paragraph IV Certification concerning one or more of the patents listed in the Orange Book.

The proposed regulations only provide a subsequent applicant with exclusivity in the event (1) the untimely filed patent is listed in the Orange Book before the Agency accepts that ANDA for filing and (2) the previous applicant withdraws its ANDA. The practical problems engendered by this proposal are demonstrated by Andrx' experience with its ANDA for generic Cardizem® CD, the pertinent chronology of which is attached as Exhibit A. This chronology shows how a Paragraph IV Certification may be directly and materially affected by subsequent listing of a patent in the Orange Book.

In this case, Andrx reformulated the product on three separate occasions in an effort to avoid infringing two subsequently listed patents. The reformulations were not required from a regulatory standpoint, as our original ANDA formulation was approved. However, we concluded that reformulations could -- they actually did -- propel resolution of patent issues, thereby avoiding unnecessary years of patent litigation and delayed generic competition. We believe this was precisely the outcome Congress intended to promote.

The time frames ultimately adopted in this provision need to (and should) reward an applicant for designing around the patents listed at the time it submits an application to the Agency. No applicant should be penalized because a patent is listed in the Orange Book after its ANDA is submitted, but before that ANDA is accepted for filing. At that later date there is no act the applicant can take to avoid that patent.

6. The Proposed Regulations Do Not Adequately Handle Cases Involving Multiple Patents.

The proposed regulations grant the one, and only, period of exclusivity to the first applicant if it prevails against the NDA holder on "any patent." As noted above, we believe that exclusivity should be awarded to any Successful Applicant. The second, and separate, problem with the "any patent" proposal is that it can award and expend exclusivity without any generic product actually being made available to the public. This anomalous result derives from the fact that NDA holders often list more than one patent. In most cases, such as current challenges to Prilosec®, Andrx and the generic applicants will be required to litigate each of those patents. We could prevail on some, and lose on others. In that situation, the proposed regulations initiate a single exclusivity period. No generic product would be available to the public, and no incentive under the statute would have been provided to encourage new Paragraph IV challenges by other applicants,

Other, similar dead-end, non-incentive examples exist. For example, under Rule 54(b) of the Federal Rules of Civil Procedure, a litigant can secure a favorable determination on one of the patents at issue in its case, while it must continue to litigate other patent issues in the same case. In this situation, the 180-day exclusivity period would begin, and probably would conclude, before the ANDA applicant secures a decision on the other patents. The regulation not only fails to provide incentives, it is in such circumstances a disincentive.

Consistent with our comments above, Andrx believes that the proposed regulations do not deal with these situations appropriately. The final regulations should award a 180-day

period of exclusivity – vis-a-vis later filed applicants – to the first ANDA applicant who prevails against (or markets its product despite) the obstacles posed by any patent which a prior applicant has failed to defeat. Such incentive rewards the public benefit secured by the applicant and is entirely appropriate under (and we believe mandated by) the statute.

7. A Subsidiary, Affiliate Or Licensee Of The Company That Owns Or Markets The Listed Drug Should Not Be Eligible for Exclusivity.

The proposed regulations do not address the potential for abuse presented by Paragraph IV ANDAs submitted by companies closely aligned with the NDA holder. The Agency is well aware that many generic drug companies are "captive" – wholly or partially owned by innovator companies. For example, Genpharm's corporate parent is Merck AG[9], and Geneva is owned by Novartis. If the first applicant with a paragraph IV certification is a "captive" generic, its parent might elect not to sue. Thus, the "captive" paragraph IV ANDA could obtain approval, and withhold commercial marketing until the patent expires, in order not to undermine the market position enjoyed by its parent. FDA Brief, Granutec v. Shalala, September 1997, at p. 28.

The triggering period mechanism reduces but does not eliminate potential abuses of the type described by the Agency. Andrx therefore proposes that the Agency issue final regulations containing provisions that (a) eliminate exclusivity in favor of the first paragraph IV applicant that is a "captive" of the innovator company, and (b) award exclusivity to the

9 Merck AG is a German corporation, unaffiliated with Merck and Co.

first non-captive paragraph IV applicant and, for the reasons previously discussed, the first Successful Applicant.

8. In Light Of The Proposed Regulations Making Each Particular Strength Of A Listed Drug Product Eligible For A Separate Exclusivity Period, The Agency Should Revise Its Method Of Handling Approvals Of ANDAs With Multiple Strengths.

The Agency's proposed regulations properly recognize that different strengths of the same drug should receive separate periods of exclusivity. We note, however, that the Agency's current administrative practice in handling ANDAs that contain different strengths of a listed drug is inconsistent with certain of the objectives espoused by the proposed regulations.

ANDAs for various strengths of a drug will not necessarily include separate bioequivalence studies on each strength of the product, e.g., when the different strengths are dose proportional. In at least one such instance, the Agency refused to file an ANDA submitted by Andrx (for various strengths), based on the Agency's determination that studies were required for each strength. In response to this notification, Andrx amended its ANDA to eliminate the strength for which a filing could not be accepted. In another instance, the ANDA was accepted for filing but, when a new strength was added to the filing (based upon a newly introduced strength for the reference product), the Agency later advised that studies would be required for the additional strength. Andrx then performed a biostudy on that strength, and amended its ANDA to include that strength. The Agency now advises, however, that Andrx may not be able to have its originally filed strengths approved until the

Agency has completed its review of that additional strength, and has determined that such strength may also be approved.

Andrx believes that this administrative treatment is entirely inconsistent with the proposed regulations, which state:

> The Agency's interpretation of the statute to render ANDA's eligible for exclusivity for each particular strength of a drug product would have two results. First, it would encourage applicants vying for submission of the first application, and the concomitant reward of exclusivity, to submit ANDA's that cover the greatest number of strengths in an attempt to obtain maximum protection from other generic competitors. Second, it would prevent an ANDA applicant for only one strength of a drug product from blocking subsequent applicants with other strengths of the drug product from entering the market. Thus, FDA's interpretation would encourage prompt entry into the market of the greatest number of strengths of a particular drug product.

9. The Proposed Regulations Should Clarify When A New Paragraph IV Certification Is Required And The Applicable Procedures.

The proposed regulations make the following statement:

"[I]f the first applicant submits a new paragraph IV certification because, for example, it makes a formulation change requiring a supplement or amendment to its ANDA, it may no longer be accorded first applicant status."

Andrx believes that the elimination of exclusivity in the circumstance cited above is both unlawful and unnecessary, for the reasons previously described in this letter. In addition, Andrx believes that the regulations should be clarified to better describe the circumstances in which an applicant is required to submit a new paragraph IV certification, and the consequences of that action,

As demonstrated by the attached Exhibit A, Andrx was unaware that the ANDA supplement it filed in September 1998 (containing the bioequivalence studies Andrx performed pursuant to the Agency's instruction), would require Andrx to make a new Paragraph IV certification to the NDA holders of Cardizem® CD. The Agency only advised Andrx of this requirement in January 1999 and cited 21 CFR §§3 14.71(c) and 3 14.52(d) as the controlling authorities. These provisions require that a new Paragraph IV certification be made to the Agency. They do not, however, require the applicant to make a new Paragraph IV certification to the NDA holders, nor do they specify the procedures to be followed in connection with that new certification or the consequences thereof.

For these reasons, upon learning of the Agency's interpretation of its regulations, Andrx advised the Agency of the following:

> "As discussed . . . Andrx does not believe [a new] Paragraph IV Certification is legally required. Despite this belief, Andrx is submitting the enclosed certification based upon the following representations and understandings:
>
> 1. As the FDA procedures do not provide for a notice of acceptance of filing of a supplement, which is the event that triggers the notice to the parties having an interest in the referenced product, Andrx is authorized to immediately forward the detailed explanation of its Paragraph IV Certification to . . . ; and
>
> 2. The Andrx supplement has been assigned ANDA #74-752, the same ANDA number as our application that was approved on July 9, 1998, and thus, such application and this supplement remain fully entitled to the 180-day period of marketing exclusivity accorded to Andrx pursuant to Section 355(j)(5)(B)(iv)."

Thus, Andrx believes that the proposed regulations should be amended to specifically indicate the circumstances under which a new Paragraph IV Certification is to be sent to the

NDA holders, the time frame in which that certification is to be sent, a procedure whereby the Agency (i) confirms whether the supplement (and the bioequivalence studies contained therein) is to remedy an approval problem or is required for some other reason (assuming the Agency accepts our proposition that exclusivity should not be lost in every new biostudy situation), and (ii) specifies how and whether the 30-month period applicable to any lawsuit which resulted from the first certification will be affected by any lawsuit which is filed (or not filed) by the NDA holder with respect to the second certification.

Please contact the undersigned if you believe any further clarification of these points would be necessary or desirable.

Sincerely,

Scott Lodin
Vice President and General Counsel

Exhibit A

CHRONOLOGY OF EVENTS SURROUNDING CARDIZEM® CD ANDA

January 1992	Cardizem® CD is first marketed;
February 1994	Andrx has pilot biostudy data and is preparing to commence formal bioequivalence studies for its ANDA product;
February 1994	Patent #5,286,497 (the "497 patent"), an untimely patent, is issued and listed in the Orange Book;
March 1994	Andm begins to reformulate its product so that it will not infringe the 497 patent;
September 1995	Andrx submits an ANDA with a Paragraph IV Certification to FDA and provides patent information to NDA holders on an informal basis, to avoid litigation delays;
November 1995	Patent #5,470,584 (the "584 patent"), a new untimely patent, is issued;
November 1995	FDA issues Notice of Acceptance of the Andrx ANDA;
December 1995	Andrx receives Notice of Acceptance and sends Paragraph IV certification to the reference drug entities;
January 1996	The 584 patent is listed in the Orange Book;

September 1997	FDA grants tentative approval of the Andrx ANDA;
November 1997	Andrx files minor ANDA amendment, seeking to more clearly avoid the claims of the '584 patent;
January 1998	FDA notifies Andrx that new bioequivalence studies will be required for the Andrx minor amendment and Andrx withdraws its amendment;
July 1998	FDA declares Andrx ANDA approval as effective;
September 1998	Andrx supplements its approved ANDA with the requested additional bioequivalence studies;
January 1999	FDA notifies Andrx that a new Paragraph IV certification is required to be sent to the reference drug entities; and
June 1999	FDA approves ANDA supplement, the patent litigation is settled, and sale of generic product commences.

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